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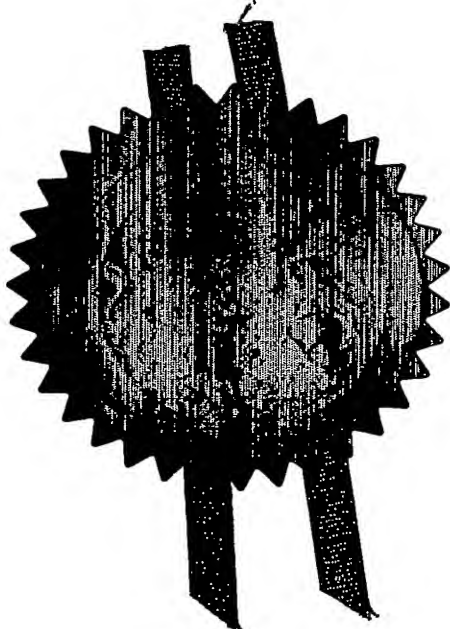
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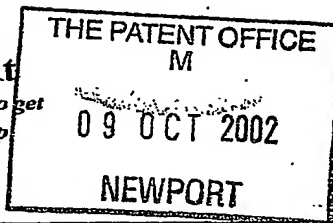




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The Patent Office

Cardiff Road
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1. Your reference

100853

2. Patent application number

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3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number (if you know it)

7822448003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

THERAPEUTIC TREATMENT

5. Name of your agent (if you have one)

Lucy Clare Padgett

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number (if you know it)

8340762001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

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 - b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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08/10/2002

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Jennifer C Bennett - 01625 230148

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THERAPEUTIC TREATMENT

The present invention relates to the use of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof in the treatment or prevention of headache that results from administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof. The present invention further relates to a combination comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof.

Cancer affects an estimated 10 million people worldwide. This figure includes incidence, prevalence and mortality. More than 4.4 million cancer cases are reported from Asia, including 2.5 million cases from Eastern Asia, which has the highest rate of incidence in the world. By comparison, Europe has 2.8 million cases, North America 1.4 million cases, and Africa 627,000 cases.

In the UK and US, for example, more than one in three people will develop cancer at some point in their life. Cancer mortality in the U.S. is estimated to account for about 600,000 a year, about one in every four deaths, second only to heart disease in percent of all deaths, and second to accidents as a cause of death of children 1-14 years of age. The estimated cancer incidence in the U.S. is now about 1,380,000 new cases annually, exclusive of about 900,000 cases of non-melanotic (basal and squamous cell) skin cancer.

Cancer is also a major cause of morbidity in the UK with nearly 260,000 new cases (excluding non-melanoma skin cancer) registered in 1997. Cancer is a disease that affects mainly older people, with 65% of cases occurring in those over 65. Since the average life expectancy in the UK has almost doubled since the mid nineteenth century, the population at risk of cancer has grown. Death rates from other causes of death, such as heart disease, have fallen in recent years while deaths from cancer have remained relatively stable. The result is that 1 in 3 people will be diagnosed with cancer during their lifetime and 1 in 4 people will die from cancer. In people under the age of 75, deaths from cancer outnumber deaths from diseases of the circulatory system, including ischaemic heart disease and stroke. In 2000, there were 151,200 deaths from cancer. Over one fifth (22 per cent) of these were from lung cancer, and a quarter (26 per cent) from cancers of the large bowel, breast and prostate.

Worldwide, the incidence and mortality rates of certain types of cancer (of stomach, breast, prostate, skin, and so on) have wide geographical differences which are attributed to racial, cultural, and especially environmental influences. There are over 200 different types of

cancer but the four major types, lung, breast, prostate and colorectal, account for over half of all cases diagnosed in the UK and US. Prostate cancer is the fourth most common malignancy among men worldwide, with an estimated 400,000 new cases diagnosed annually, accounting for 3.9 percent of all new cancer cases.

5 Current options for treating cancers include surgical resection, external beam radiation therapy and / or systemic chemotherapy. These are partially successful in some forms of cancer, but are not successful in others. Recently, endothelin A receptor antagonists have been identified as potentially of value in the treatment of cancer (Cancer Research, 56, 663-668, February 15th, 1996 and Nature Medicine, Volume 1, Number 9, September 1999, 944-949).

10 The endothelins are a family of endogenous 21 amino acid peptides comprising three isoforms, endothelin-1, endothelin-2 and endothelin-3. The endothelins are formed by cleavage of the Trp²¹-Val²² bond of their corresponding proendothelins by an endothelin converting enzyme. The endothelins are among the most potent vasoconstrictors known and have a characteristic long duration of action. They exhibit a wide range of other activities
15 including cell proliferation and mitogenesis, extravasation and chemotaxis, and also interact with a number of other vasoactive agents.

The endothelins are released from a range of tissue and cell sources including vascular endothelium, vascular smooth muscle, kidney, liver, uterus, airways, intestine and leukocytes. Release can be stimulated by hypoxia, shear stress, physical injury and a wide range of
20 hormones and cytokines. Elevated endothelin levels have been found in a number of disease states in man including cancers.

However, the administration of endothelin receptor antagonists is known to result in headaches in man. Administration to man of Bosentan (TracleerTM) at the recommended dose of 125-250mg bid, this endothelin receptor antagonist induces headaches in 22% of subjects
25 as reported in the prescribing information (Physicians Desk Reference, 2002). The incidence of headache in cancer patients receiving therapy with another endothelin receptor antagonist, Atrasentan, is cited at 50-100% of subjects, at doses of 20mg and above (Carducci, 2002). With respect to this latter citation, "the headache began with the initiation of therapy and resolved after several days of atrasentan treatment... These headaches were controlled, as
30 necessary with standard analgesic therapy".

ZD4054 is an endothelin receptor antagonist which has recently commenced clinical testing, and which also induces headaches in man. Based on citations by Carducci (Carducci, 2002) a number of "standard analgesic therapies" were tried, including Paracetamol,

Ibuprofen and Codeine to treat the ZD4054 induced headaches. Despite standard analgesic therapy, several subjects still reported persistent headache. Surprisingly, administration of the 5HT_{1B/1D} agonist zolmitriptan (sold under the trademark Zomig), licensed for the treatment of migraine, proved effective in reducing the intensity of ZD4054 induced headaches in subjects
5 in which standard analgesic therapy had already failed.

During migraine excessive cerebrovascular dilation and neurogenic inflammatory processes are considered to contribute to pain. The 5-HT_{1B/1D}-receptors mediate cerebrovascular vasoconstriction and inhibit neurogenic inflammation. 5-HT_{1B/1D} receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein
10 vasoconstriction and neurogenic inflammation in the cerebrovascular bed is indicated.

The present invention relates to the use of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof in the treatment or prevention of headaches that result from administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof.

15 According to a further feature of the present invention, there is provided a combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof.

Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention
20 "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of the synergistic effect of the combination.

25 Where the term "headache" is referred to it is to be understood that this term includes headaches, migraines, cluster headaches and headache associated with vascular disorders.

Where cancer is referred to, particularly it refers to oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, kaposi sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma,
30 lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, renal cancer, brain cancer, lymphoma and leukaemia. More particularly it refers to prostate cancer. In addition, more particularly it refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and / or breast cancer. Furthermore, more

particularly it refers to bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and / or renal cancer. In another embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces metastases to the bone. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more
5 particularly the cancer produces skin metastases.

Where the "treatment or prevention of headache" is referred it is to be understood that this refers to the treatment or prevention of headaches and related conditions for example providing pain relief, decreasing nausea, decreasing photophobia and phonophobia.

Suitable compounds, or a pharmaceutically acceptable salt thereof, possessing
10 endothelin receptor antagonist activity include those described in US 5292740, US 5334598, US 5378715, US 5389620, US 5420123, US 5464853, US 5482960, US 5514691, US 5514696, US 5541186, US 55543521, US 5559105, US 5571821, US 5780473, US 5962490, US 5965732, US 6080774, US 6420567, US 2002091272(A1), WO 93/08799, WO 93/21219, WO 93/23404, WO 93/25580, WO 94/02474, WO 94/03483, WO 94/14434, WO 94/21259,
15 WO 94/21590, WO 94/24084, WO 94/25013, WO 94/27979, WO 95/03044, WO 95/03295, WO 95/04530, WO 95/04534, WO 95/05372, WO 95/05374, WO 95/05376, WO 95/08989, WO 95/12611, WO 95/13262, WO 95/15944, WO 95/15963, WO 96/20177, WO 95/26360, WO 95/26716, WO 95/26360, WO 95/26957, WO 95/33748, WO 95/33752, WO 95/35107, WO 96/04905, WO 96/06095, WO 96/07653, WO 96/08483, WO 96/08486, WO 96/08487,
20 WO 96/09818, WO 96/11914, WO 96/11927, WO 96/12706, WO 96/15109, WO 96/19455, WO 96/19459, WO 96/22978, WO 96/23773, WO 96/30358, WO 96/31492, WO 96/33170, WO 96/33190, WO 96/40681, WO 97/30045, WO 98/09953, WO 95/08550, WO 98/49162, WO 99/06397, WO 01/49685, WO 02/64573, EP 436189, EP 496452, EP 510526, EP 526708, EP 552417, EP 555537, EP 601386, EP 617001, EP 628569, EP 633259, EP 658548,
25 EP 682016, EP 713875, EP 702012, EP 733626, EP 743307, EP 749964, GB 2266890, GB 2275926, GB 2276383, GB 2277446, GB 2295616, DE 4341663, JP 6256261, JP 6122625, JP 7330622, JP 7133254, JP 8059635, JP 7316188, and JP 7258098 and the endothelin receptor antagonists described therein, particularly those described in claim 1 and the named examples, of the above patents and applications, are incorporated herein by reference.

30 Additional suitable compounds, or a pharmaceutically acceptable salt thereof, possessing endothelin receptor antagonist activity include those described in the J Med Chem papers 1996, 39, 2123-2128; 1997, 40, 3, 322-330; 2001, 44, 1211-1216; 2001, 44, 3978-3984

and the endothelin receptor antagonists described therein are also incorporated herein by reference.

Further suitable compounds, or a pharmaceutically acceptable salt thereof, possessing endothelin receptor antagonist activity include A-127722, atrasentan (ABT-627), BQ-123, BQ-788, BMS 182874, feloprentan (BSF 420627), FR139317, IPI-950, L-749,329, L-754,142, LU 110896, LU 110897, PD 156707, PD 155080, Ro 46-2005, bosentan (Ro 47-0203), SB 217242, SB 209670, TAK-044, YM598, sitaxsentan (TBC11251), ZD1611, ambrisentan, tezosentan, darusentan, *N*-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulphonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide and *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054).

A particular compound possessing endothelin receptor antagonist activity is atrasentan (ABT-627) or a pharmaceutically acceptable salt thereof. A particular compound possessing endothelin receptor antagonist activity is YM598 or a pharmaceutically acceptable salt thereof. A particular compound possessing endothelin receptor antagonist activity is ZD4054 or a pharmaceutically acceptable salt thereof. A particular compound possessing endothelin receptor antagonist activity is ZD1611 or a pharmaceutically acceptable salt thereof.

In another aspect of the invention the endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is an endothelin A receptor antagonist. In a further aspect of the invention, the endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is an endothelin B receptor antagonist. In an additional aspect of the invention, the endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, is a mixed endothelin A and B receptor antagonist.

Suitable compounds, or a pharmaceutically acceptable salt thereof, possessing 5-HT_{1B/1D} receptor agonist activity include those described in EP 486666, WO 97/06162 and these 5-HT_{1B/1D} receptor agonists, particularly those of claim 1 and the named examples of these patents and applications, are incorporated herein by reference.

Particular classes of 5-HT_{1B/1D} receptor agonists are the triptans, or a pharmaceutically acceptable salt thereof.

Further particular compounds, or pharmaceutically acceptable salts thereof, possessing 5-HT_{1B/1D} receptor agonist activity include zolmitriptan, sumatriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and almotriptan. Particularly the compound, or a pharmaceutically acceptable salt thereof, possessing 5-HT_{1B/1D} receptor agonist activity is zolmitriptan ((S)-4-

{3-[2-(dimethylaminoethyl)-1H-indol-5-yl]methyl]-2-oxazolidinone), or a pharmaceutically acceptable salt thereof.

Particular combinations of the present invention include:

- ZD4054, or a pharmaceutically acceptable salt thereof, and zolmitriptan, or a pharmaceutically acceptable salt thereof;
- ZD1611, or a pharmaceutically acceptable salt thereof, and zolmitriptan, or a pharmaceutically acceptable salt thereof;
- atrasentan, or a pharmaceutically acceptable salt thereof, and zolmitriptan, or a pharmaceutically acceptable salt thereof; and
- YM598, or a pharmaceutically acceptable salt thereof, and zolmitriptan, or a pharmaceutically acceptable salt thereof.

Further particular combinations include the four identified immediately above but wherein zolmitriptan is replaced with one of sumatriptan, eletriptan, frovatriptan, naratriptan, rizatriptan or almotriptan.

Suitable pharmaceutically-acceptable salts include, for example, salts with alkali metal (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, for those compounds which are sufficiently basic, suitable pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid. Alternatively, the compounds may exist in zwitterionic form.

In subjects with ZD4054 induced headache, a dose of 2.5-5mg zolmitriptan administered orally was found to be effective in reducing the severity of headache where standard analgesic therapy had failed.

According to the present invention, there is provided the use of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in the treatment or prevention of headache that results from administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof.

In this aspect of the invention, there is provided the use of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of headache that results from administering an endothelin receptor

antagonist, or a pharmaceutically acceptable salt thereof, in a warm-blooded animal, such as man.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment or prevention of headache that results from administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof.

In this aspect of the invention, there is provided a method of treating or preventing headaches that result from administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, which comprises administering a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, to a warm-blooded animal, such as man.

In a further aspect of the present invention, there is provided a combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof for use as a medicament.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

Therefore according to the present invention, there is provided a method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof in combination with an effective amount of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof.

According to a further aspect of the present invention there is provided a kit comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof,

and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof; optionally with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- 5 a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;
- b) a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- 10 d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- 15 b) a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

According to a further aspect of the invention there is provided a pharmaceutical
20 composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to a further aspect of the invention there is provided a pharmaceutical
25 composition which comprises an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

30 The pharmaceutical compositions may be in a form suitable for oral administration, for example as a tablet or capsule (conventional or "fast-melt"), for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream, for rectal

administration or as a nasal spray formulation. In general the above compositions may be prepared in a conventional manner using conventional excipients and according to methods generally known in the art of formulation technology. For example formulations of the 5-HT_{1B/1D} receptor agonist zolmitriptan may be prepared according to EP 486666, WO 01/39772, US 5,178,878, US 6,024,981.

According to a further aspect of the present invention there is provided a kit comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof; optionally with instructions for use; for use in the treatment of cancer.

According to a further aspect of the present invention there is provided a kit comprising:

- a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;
 - b) a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof; in a second unit dosage form; and
 - c) container means for containing said first and second dosage forms; and optionally
 - d) with instructions for use;
- for use in the treatment of cancer.

According to a further aspect of the present invention there is provided a kit comprising:

- a) an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
 - b) a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in a second unit dosage form; and
 - c) container means for containing said first and second dosage forms; and optionally
 - d) with instructions for use;
- for use in the treatment of cancer.

According to another feature of the invention there is provided the use of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in combination with a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, in combination with a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in the treatment of cancer, in a warm-blooded animal, such as man.

5 According to a further aspect of the present invention there is provided a combination comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

10 According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man
15 in need of such therapeutic treatment for use in the treatment of cancer.

The endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose of 1g or less daily and this would be expected to provide a therapeutically-effective dose. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration,
20 and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The 5-HT_{1B/1D} receptor agonist, or pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose, for example, from about 0.5 mg to 15 mg (for example, 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10 mg) of active
25 ingredient. When the 5-HT_{1B/1D} receptor agonist is zolmitriptan, a conventional tablet formulation may be used for oral administration containing 2.5 mg or 5 mg of active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any
30 particular patient.

The dosage of each of the two drugs and their proportions have to be composed so that the best possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

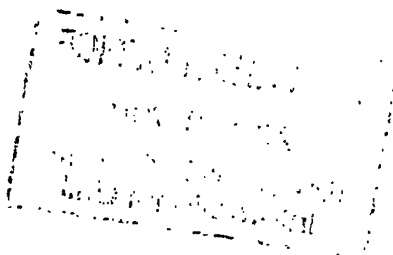
Claims

1. The use of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in the treatment or prevention of headache that results from administering an endothelin
5 receptor antagonist, or a pharmaceutically acceptable salt thereof.
2. The use of a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of headache that results from administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt
10 thereof, in a warm-blooded animal, such as man.
3. A pharmaceutical composition which comprises a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment or prevention of headache that results from
15 administering an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof.
4. A combination, comprising an endothelin receptor antagonist, or a pharmaceutically acceptable salt thereof, and a 5-HT_{1B/1D} receptor agonist, or a pharmaceutically acceptable salt thereof.
20
5. The combination according to claim 4 wherein the endothelin receptor antagonist is selected from A-127722, atrasentan (ABT-627), BQ-123, BQ-788, BMS 182874, feloprentan (BSF 420627), FR139317, IPI-950, L-749,329, L-754,142, LU 110896, LU 110897, PD 156707, PD 155080, Ro 46-2005, bosentan (Ro 47-0203), SB 217242, SB 209670, TAK-044,
25 YM598, sitaxsentan (TBC11251), ZD1611, ambrisentan, tezosentan, darusentan, *N*-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulphonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-*N*,3,3-trimethylbutanamide and *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054) or a pharmaceutically acceptable salt thereof.
- 30 6. The combination according to claims 4 or 5 wherein the 5-HT_{1B/1D} receptor agonist is selected from zolmitriptan, sumatriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and almotriptan or a pharmaceutically acceptable salt thereof.

7. The combination according to any one of claims 4-6 wherein the endothelin receptor antagonist is ZD4054, or a pharmaceutically acceptable salt thereof, and the 5-HT_{1B/1D} receptor agonist is zolmitriptan, or a pharmaceutically acceptable salt thereof.
- 5 8. The combination according to any one of claims 4-7 for use as a medicament.
9. A pharmaceutical composition comprising the combination according to any one of claims 4-7, in association with a pharmaceutically acceptable diluent or carrier.
- 10 10. The use of the combination according to claims 4-7, in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

ABSTRACT**Title: Therapeutic Treatment**

- 5 The use of a 5-HT_{1B/1D} receptor agonist in the treatment or prevention of headache that results from administering an endothelin receptor antagonist; and the combination, comprising an endothelin receptor antagonist and a 5-HT_{1B/1D} receptor agonist is described.



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